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?b 155
       20sep93 09:50:37 User208669 Session D543.2
            $0.10    0.001 Hrs File5
     $0.10  Estimated cost File5
     $0.01  DIALNET
     $0.11  Estimated cost this search
     $0.40  Estimated total session cost    0.008 Hrs.

File 155:MEDLINE  1966-1993/NOV (9311W2)

      Set  Items  Description
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?s her2 or neu or p185 or c(w)erbb
              93  HER2
             960  NEU
             106  P185
          345578  C
            1168  ERBB
             542  C(W)ERBB
      S1    1441  HER2 OR NEU OR P185 OR C(W)ERBB
?s insulin(w)receptor or (igf or insulin(w)like(w)growth(w)factor)(w)receptor
          105970  INSULIN
          179748  RECEPTOR
            3217  INSULIN(W)RECEPTOR
            4607  IGF
          105970  INSULIN
          125471  LIKE
          331432  GROWTH
          221383  FACTOR
            6780  INSULIN(W)LIKE(W)GROWTH(W)FACTOR
          179748  RECEPTOR
             264  (IGF OR INSULIN(W)LIKE(W)GROWTH(W)FACTOR)(W)RECEPTOR
      S2    3422  INSULIN(W)RECEPTOR OR (IGF OR
                  INSULIN(W)LIKE(W)GROWTH(W)FACTOR)(W)RECEPTOR
?s (egf or epidermal(w)growth(w)factor)(w)receptor
            6467  EGF
           24654  EPIDERMAL
          331432  GROWTH
          221383  FACTOR
           10864  EPIDERMAL(W)GROWTH(W)FACTOR
          179748  RECEPTOR
      S3    3037  (EGF OR EPIDERMAL(W)GROWTH(W)FACTOR)(W)RECEPTOR
?s s1 or s2 or s3
            1441  S1
            3422  S2
            3037  S3
      S4    7537  S1 OR S2 OR S3
?s truncat?
      S5   96317  TRUNCAT?
?s s4 and s5
            7537  S4
           96317  S5
      S6     481  S4 AND S5
?s extracellular or external or surface or ligand(w)binding or hydrophilic or
(amino or n)(w)terminal
           58123  EXTRACELLULAR
           58638  EXTERNAL
          100103  SURFACE
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        23131  LIGAND
       289365  BINDING
         4935  LIGAND(W)BINDING
         7425  HYDROPHILIC
       232041  AMINO
       235640  N
        80875  TERMINAL
        21403  (AMINO OR N)(W)TERMINAL
   S7  313465  EXTRACELLULAR OR EXTERNAL OR SURFACE OR LIGAND(W)BINDING
               OR HYDROPHILIC OR (AMINO OR N)(W)TERMINAL
?s s6 and s7
          481  S6
       313465  S7
   S8     153  S6 AND S7

?save temp
Temp SearchSave "TD198" stored

t s8/7/93 96  97 99 100 102 106 108 111 112 116 120 122 125 131 137

 8/7/93
07072077   89374077
  Secretion of the extracellular domain of the human insulin receptor from
insect cells by use of a baculovirus vector.
  Sissom J; Ellis L
  Howard Hughes Medical Institute, Dallas, TX.
  Biochem J  Jul 1 1989,  261 (1) p119-26,  ISSN 0264-6021
Journal Code: 9YO
  Languages: ENGLISH
  Document type: JOURNAL ARTICLE
  To explore the utility of the baculovirus/insect-cell system for the
expression of a soluble secreted human insulin-receptor (hIR) extracellular
ligand-binding domain, we have engineered a recombinant virus encoding an
hIR deletion mutant which is truncated eight residues from the beginning of
the predicted transmembrane domain (i.e. 921 residues). Within 24 h after
infection of Sf9 cells with virus, insulin-binding activity begins to
accumulate in the culture medium, and reaches a maximum between 48 and 72
h. The intracellular transit and processing of this secreted receptor,
designated 'AchIR01', is quite slow. After 24 h in pulse-chase experiments
approximately 50% of the metabolically labelled protein is still inside the
cell. This protein accumulates as a non-cleaved hIR precursor which is
glycosylated, but the carbohydrate is entirely endoglycosidase H
(endoH)-sensitive (i.e. high mannose). Approximately one-half of the
receptor in the culture medium (i.e. approximately 25% of the total) is in
the form of non-cleaved precursor, and about one half of its carbohydrate
chains are now endoH-resistant. The remainder of the protein is
proteolytically processed hIR (alpha-plus truncated beta-subunits). None of
these hIR species exhibit O-linked carbohydrate. Only the processed form of
the receptor in the medium binds insulin. This insulin-binding protein is
secreted as a dimer (alpha beta)2, and binds insulin with an affinity which
is comparable with that of both the wild-type hIR as well as the secreted
form of the hIR expressed in mammalian cells. Despite the rather
inefficient processing and altered glycosylation of the AchIR01 protein in
insect cells, this high-affinity insulin-binding protein accumulates in the
medium at levels (mg/litre) of about 100 times that achieved in a
mammalian-cell system.

 8/7/96
06929614   89231614
  A chimeric EGF-R-neu proto-oncogene allows EGF to regulate neu tyrosine
kinase and cell transformation.
  Lehvaslaiho H; Lehtola L; Sistonen L; Alitalo K
  Department of Virology and Pathology, University of Helsinki, Finland.
  EMBO J  Jan_1989,  8 (1) p159-66,  ISSN 0261-4189  Journal Code: EMB
  Languages: ENGLISH
```

Document type: JOURNAL ARTICLE

The neu oncogene, characterized by Weinberg and colleagues, is a transforming gene found in ethylnitrosourea-induced rat neuro/glioblastomas; its human proto-oncogene homologue has been termed erbB2 or HER2 because of its close homology with the epidermal growth factor receptor (EGF-R) gene (c-erbB1). Expression of the rat neu oncogene is sufficient for transformation of mouse NIH 3T3 fibroblasts in culture and for the development of mammary carcinomas in transgenic mice, but the neu proto-oncogene has not been associated with cell transformation. We constructed a vector for expression of a chimeric cDNA and hybrid protein consisting of the EGF-R extracellular, transmembrane and protein kinase C-substrate domains linked to the intracellular tyrosine kinase and carboxyl terminal domain of the rat neu cDNA. Upon transfection with the construct, NIH 3T3 cells gave rise to EGF-R antigen-positive cell clones with varying amounts of specific EGF binding. Immunofluorescence and immunoprecipitation using neu- and EGF-receptor specific antibodies demonstrated a correctly oriented and positioned chimeric EGF-R-neu protein of the expected apparent mol. wt on the surface of these cells. EGF or TGF alpha induced tyrosine phosphorylation of the chimeric receptor protein, stimulated DNA synthesis of EGF-R-neu expressing cells and led to a transformed cell morphology and growth in soft agar. In contrast, the neu proto-oncogene did not show kinase activity or transforming properties when expressed at similar levels in NIH 3T3 cells. (ABSTRACT TRUNCATED AT 250 WORDS)

8/7/97
06917061 89219061

Inhibition of tyrosine kinase activity of the epidermal growth factor (EGF) receptor by a truncated receptor form that binds to EGF: role for interreceptor interaction in kinase regulation.

Basu A; Raghunath M; Bishayee S; Das M
Department of Biochemistry and Biophysics, Children's Hospital of Philadelphia, Pennsylvania.

Mol Cell Biol Feb 1989, 9 (2) p671-7, ISSN 0270-7306 Journal Code: NGY
Contract/Grant No.: CA-43787; CA-15822; CA-44441
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The tyrosine kinase activity of the epidermal growth factor (EGF) receptor is regulated by a truncated receptor of 100 kilodaltons (kDa) that contains the EGF-binding site but not the kinase domain. The inhibition of kinase is not due to competition for available EGF or for the kinase substrate-binding site. Chemical cross-linking studies suggest that the 100-kDa receptor may form a heterodimer with the intact EGF receptor. Structurally related receptor kinases, such as the platelet-derived growth factor receptor, the insulin receptor, and the Neu receptor, were not inhibited by the 100-kDa receptor. The results indicate that (i) the inhibition was specific for the EGF receptor, (ii) the kinase domain had little or no role in determining target specificity, and (iii) the regulation of kinase may be due to a specific interaction of the 100-kDa receptor with the ligand-binding domain of the EGF receptor kinase.

8/7/99
06899873 89201873

Analysis of mammalian fibroblast transformation by normal and mutated human EGF receptors.

Haley JD; Hsuan JJ; Waterfield MD
Ludwig Institute for Cancer Research, London, UK.

Oncogene Mar 1989, 4 (3) p273-83, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Activation of the EGF receptor (c-erbB) tyrosine kinase has been implicated in tumorigenesis, either by overexpression of the normal receptor in the presence of EGF, or through expression of a truncated receptor lacking the EGF binding domain as in the viral oncogene v-erbB. Here, normal and truncated human EGF receptors expressed in Rat1

fibroblasts were analysed for receptor tyrosine kinase activity and several transformation parameters in comparison with polyoma middle T and EJ-ras. Expression of a truncated EGF receptor lacking the extracellular ligand binding domain induced transformation of immortalized rodent fibroblasts and appears to activate the intrinsic tyrosine kinase. The transformed phenotype becomes enhanced by further truncation of the C-terminal domain containing the tyrosine autophosphorylation sites P1 and P2. Over expression of EGF receptors with an intact extracellular region in transfected Rat1 cells shows EGF dependent transformation, which is reduced by C-terminal truncation. Transformation is dependent on the cellular receptor concentration and can be selected as a stable phenotype. We conclude that expression of receptors with a truncated EGF-binding domain alone is sufficient to transform mammalian fibroblasts, in contrast to chick fibroblasts transformed by v-erbB where additional deletion of C-terminal receptor sequences appears to be an absolute requirement.

8/7/100
06860036 89162036
Structure and function of human amphiregulin: a member of the epidermal growth factor family.
Shoyab M; Plowman GD; McDonald VL; Bradley JG; Todaro GJ
Oncogen, Seattle, WA 98121.
Science Feb 24 1989, 243 (4894 Pt 1) p1074-6, ISSN 0036-8075
Journal Code: UJ7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The complete amino acid sequence of amphiregulin, a bifunctional cell growth modulator, was determined. The truncated form contains 78 amino acids, whereas a larger form of amphiregulin contains six additional amino acids at the amino-terminal end. The amino-terminal half of amphiregulin is extremely hydrophilic and contains unusually high numbers of lysine, arginine, and asparagine residues. The carboxyl-terminal half of amphiregulin (residues 46 to 84) exhibits striking homology to the epidermal growth factor (EGF) family of proteins. Amphiregulin binds to the EGF receptor but not as well as EGF does. Amphiregulin fully supplants the requirement for EGF or transforming growth factor-alpha in murine keratinocyte growth, but it is a much weaker growth stimulator in other cell systems.

8/7/102
06794860 89096860
Proviral insertional activation of c-erbB: differential processing of the protein products arising from two alternate transcripts.
Maihle NJ; Raines MA; Flickinger TW; Kung HJ
Department of Molecular Biology and Microbiology, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106.
Mol Cell Biol Nov 1988, 8 (11) p4868-76, ISSN 0270-7306
Journal Code: NGY
Contract/Grant No.: HD07104-11; CA-39207; P30 CA-43703
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Proviral insertional activation of c-erbB results in the expression of two alternate transcripts (ENV+ and ENV-). We used cDNA clones representing the two alternate transcripts to generate stably transformed quail fibroblast cell lines which express the products of these transcripts independently. Analysis of the co- and posttranslational processing of the insertionally activated c-erbB products expressed in these cell lines revealed that the protein products of the ENV+ and ENV- transcripts were processed differently. The ENV+ transcript produced a primary translation product which was rapidly cotranslationally cleaved near the amino terminus to form a 79,000-Mr product. This protein product was efficiently converted to a higher-molecular-weight form, of between 82,000 and 88,000 (gp82-88), which was terminally glycosylated and expressed on the cell surface. A small portion of the ENV+ primary translation product underwent a second proteolytic cleavage to generate an unglycosylated 53,000-Mr species. In contrast, the primary translation product of the ENV- transcript, p80, was

not proteolytically processed; this precursor form was rapidly converted to two discrete glycosylation intermediates, gp82 and go84. Only a small portion (less than 10%) of the total ENV- insertionally activated c-erbB product was slowly converted to the terminally glycosylated cell surface form, gp85-88. The processing differences that distinguished the ENV+ and ENV- products were similar to processing differences that we observed in parallel studies on the viral erbB products of the avian erythroblastosis viruses AEV-H and AEV-R, respectively. (ABSTRACT TRUNCATED AT 250 WORDS)

8/7/106
06728600 89030600
Truncation of the human EGF receptor leads to differential transforming potentials in primary avian fibroblasts and erythroblasts.
Khazaie K; Dull TJ; Graf T; Schlessinger J; Ullrich A; Beug H; Vennstrom B
Differentiation Programme, European Molecular Biology Laboratory, Heidelberg, FRG.
EMBO J Oct 1988, 7 (10) p3061-71, ISSN 0261-4189 Journal Code: EMB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The transforming capacity of the normal and mutant human EGF receptor (EGFR) was investigated in primary chicken cells. In fibroblasts, both N- and C-terminal truncations resulted in a weak, additive oncogenic activity. However, not even double truncations caused a v-erbB-like phenotype. Upon EGF-binding, on the other hand, both normal and C-terminally truncated EGFRs resembled v-erbB in their fibroblast transforming potential. In erythroblasts, N-terminal truncation was sufficient to induce constitutive self-renewal, which was enhanced by deletion of 32 C-terminal amino acids but abolished by a larger truncation of 202 amino acids. In contrast to the normal EGFR, the receptor lacking 32 C-terminal amino acids resembled v-erbB in conferring erythropoietin independence for spontaneous differentiation to the transformed erythroblasts. Our results indicate that the C-terminal domain of the EGFR is non-essential in fibroblast transformation, but seems to be crucial for both self renewal induction and specificity of receptor function in erythroblasts.

8/7/108
06715228 89017228
Properties of the insulin receptor ectodomain.
Johnson JD; Wong ML; Rutter WJ
Hormone Research Institute, University of California, San Francisco 94143.
Proc Natl Acad Sci U S A Oct 1988, 85 (20) p7516-20, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: DK37661
Languages: ENGLISH
Document type: JOURNAL ARTICLE
To study the properties of the extracellular insulin-binding domain of the human insulin receptor (hIR), we have expressed portions of the parent molecule in mammalian cells. Receptor cDNAs encoding the entire hIR ectodomain, the alpha subunit of the hIR alone, or a portion of the alpha subunit containing the cysteine-rich region were placed within an expression vector and in turn used to transfect CHO cells. Only cells expressing mRNA for the entire hIR ectodomain secreted hIR-related protein, suggesting that the truncated versions of this domain are unstable. The ectodomain molecules were extensively glycosylated, properly processed heterotetramers. Further, they bound insulin with an affinity similar to that of the intact hIR. In the electron microscope the secreted ectodomains appeared as discrete globular structures. After incubation with roughly equimolar quantities of insulin, the ectodomains associated to form loops or branched and folded linear macroarrays. However, these structures were not restricted to the specific ligand, insulin, since epidermal growth factor also produced the effect. Nevertheless, it seems that the receptor ectodomains can exist in two structural states. The conversion of the singular to the aggregated state may somehow be associated with transmembrane communication and activation of the biological response.

8/7/111
06685708 88330708
Analysis of structure and activation of some receptor-type tyrosine kinase oncogenes.
Shibuya M; Matsushime H; Yamazaki H; Wang LH; Fukui Y; Ueyama Y; Tamaoki N
Institute of Medical Science, University of Tokyo, Japan.
Int Symp Princess Takamatsu Cancer Res Fund 1986, 17 p195-202,
Journal Code: HHI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We first describe the characterization of proto-oncogene of v-ros in chicken and human genomes. v-ros sequence of UR2 avian sarcoma virus carries a hydrophobic short stretch upstream of the kinase domain, suggesting that its proto-oncogene encodes for a receptor molecule. Using v-ros DNA as a probe we isolated chicken and human c-ros proto-oncogenes. These c-ros DNAs contained a tyrosine kinase domain, transmembrane domain and a part of an extracellular domain carrying an N glycosylation site which was not acquired by UR2 sarcoma virus. These results strongly suggest that proto-oncogene c-ros encodes for a receptor of cell growth or differentiation factor(s) and that the v-ros sequence is a truncated form of this receptor molecule. Structural alteration and overexpression under the control of viral promoter may be crucial for transforming activity of v-ros gene. We then report another example where a receptor-type oncogene is qualitatively and quantitatively activated. By screening with various onc probes we detected two human glioblastomas which have amplification of structurally altered c-erbB1 (epidermal growth factor (EGF) receptor) gene. c-erbB1 gene in these tumors bears a small deletion within the extracellular domain, and the gene product 140 kd protein shorter than the normal 170 kd EGF receptor was heavily phosphorylated on tyrosine residue even without ligand in in vitro phosphorylation reaction. Thus, these mutated EGF receptors seem to be fixed as a "switch-on" form in signal transduction for cell growth and might be involved in the transformation of glial cells.

8/7/112
06685707 88330707
Altered expression of epidermal growth factor receptors in human bladder and lung tumours.
Berger MS; Greenfield C; Waterfield MD
Ludwig Institute for Cancer Research, Middlesex Hospital/University College Branch, London, U.K.
Int Symp Princess Takamatsu Cancer Res Fund 1986, 17 p183-94,
Journal Code: HHI
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
The expression of epidermal growth factor (EGF) receptors on 31 primary bladder and 109 lung tumours was evaluated by immunohistology using two monoclonal antibodies which recognise either the external ligand binding domain or the internal tyrosine kinase domain. At the immunocytochemical level receptor over-expression was detected at a higher frequency in squamous lung tumours than in other types of lung tumours. In the bladder tumours those with the highest level of EGF receptor expressions were invasive and poorly differentiated. In all tumours similar receptor expression levels were detected with both antibodies indicating that expression of truncated receptors is not detectable by this method. Analysis of DNA from the bladder and lung tumours failure to show gene re-arrangement, except in one unusual case of a carcinosarcoma, thus confirming these histochemical results. Gene amplification accompanied by massive overexpression of receptors was found in 1 of 29 bladder tumours and in 2 of 10 squamous cell carcinomas of the lung. The results suggest that analysis of receptor overexpression could prove useful for diagnosis of certain tumours. (30 Refs.)

8/7/116

06378414 88223414

Biosynthesis of the epidermal growth factor receptor in human squamous cell carcinoma lines: secretion of the truncated receptor is not common to epidermal growth factor receptor-hyperproducing cells.

Gamou S; Hirai M; Rikimaru K; Enomoto S; Shimizu N

Department of Molecular Biology, Keio University School of Medicine, Tokyo, Japan.

Cell Struct Funct Feb 1988, 13 (1) p25-38, ISSN 0386-7196 Journal Code: CSF

Contract/Grant No.: GM24375

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The biosynthesis of the EGF receptor was examined in the epidermoid carcinoma cell line A431 and five novel cell lines from human squamous cell carcinomas possessing high numbers of EGF receptors. Newly synthesized EGF receptors were visualized by labeling with [35S]methionine and immunoprecipitation with a monoclonal anti-EGF receptor antibody. In addition, the processing of the EGF receptor and its intracellular transport was analyzed by distinguishing cell surface receptors from intracellular receptors and by treating cells with inhibitors such as tunicamycin, monensin and brefeldin A. These analyses revealed that in all the tumor cell lines the EGF receptor is synthesized as a glycosylated protein of Mr 160,000 which is converted to the receptor of Mr 170,000 through posttranslational glycosylation. The receptors of Mr 160,000 and 170,000 appeared to possess high mannose type oligosaccharide chains because endoglycosidase H treatment reduced their molecular weights by approximately 30,000. A431 was the only tumor cell line studied that secreted the truncated EGF receptor of Mr 110,000. In A431 cells, the truncated EGF receptor was generated from a protein of Mr 60,000 through tunicamycin- and monensin-sensitive glycosylation. A431 cells treated with monensin secreted the truncated receptor as a Mr 95,000 form.

8/7/120

06432499 88077499

Polypeptide growth factors: roles in normal and abnormal cell growth.

Deuel TF

Department of Medicine and Biological Chemistry, Jewish Hospital at Washington University Medical Center, St. Louis, Missouri 63110.

Annu Rev Cell Biol 1987, 3 p443-92, ISSN 0743-4634 Journal Code: ARB

Contract/Grant No.: HL31102; HL14147

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC

An increasing number of polypeptide growth factors have been identified that regulate not only cell proliferation but an extraordinary range of cell activities, including matrix protein deposition and resolution, the maintenance of cell viability, cell differentiation, inflammation, and tissue repair. Normal cells appear to require growth factors for proliferation and for maintenance of viability. Cells that secrete a polypeptide growth factor have an advantage in growth. These factors can act either externally through cell surface receptors or perhaps internally during the transport of receptors and growth factors through the ER and Golgi, causing autocrine stimulation of cell growth. Depending on the cell type, growth factors can also be potent inhibitors of cell growth rather than stimulating growth, and the effects can depend on the presence or absence of other growth factors. Platelet-derived growth factor has been shown to be nearly identical to the product of the v-sis gene of the simian sarcoma virus, which appears to cause cell transformation through its interactions with the PDGF receptor activating the tyrosine kinase activity of the PDGF receptor. Similarly, two proto-oncogenes, c-erbB and c-fms, encode growth factor receptors. The EGF receptor activity of the v-erb oncogene product appears to be constitutively activated without the need for growth factor, perhaps because of the truncation at the amino terminus deleting the EGF binding domain. The induction of the myc and the fos proteins by growth factor stimulation of quiescent cells, as well as the potential for the p21 product of the ras oncogene to act as an intermediate

in transducing adrenergic signals, provide direct evidence that these pathways are important for stimulation of cell growth. Cells transformed by the v-sis oncogene always appear to bear PDGF cell surface receptors, which suggests that this oncogene has a specific requirement of the PDGF receptor for transformation. In contrast, cells transformed by the v-erbB and v-fms oncogenes are not stimulated by EGF or by CSF-1. Thus it seems likely that the tyrosine kinase activity of the corresponding receptor is ubiquitously expressed in these cases. Major questions remain unanswered. In particular, what are the mechanisms by which growth factors initiate pathways leading to DNA synthesis? What are the physiological substrates of the growth factor receptor tyrosine kinase? Considerable effort also is needed to further define the cellular specificity of the different growth factors, particularly within intact tissues, and to determine how the various growth factors interact.(ABSTRACT TRUNCATED AT 400 WORDS) (434 Refs.)

8/7/122
06278934 87252934
Transmembrane signaling of interleukin 2 receptor. Conformation and function of human interleukin 2 receptor (p55)/insulin receptor chimeric molecules.
Hatakeyama M; Doi T; Kono T; Maruyama M; Minamoto S; Mori H; Kobayashi M; Uchiyama T; Taniguchi T
J Exp Med Aug 1 1987, 166 (2) p362-75, ISSN 0022-1007
Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Chimeric genes were constructed which gave rise to the expression of novel receptor molecules consisting of the extracellular domain of the human interleukin 2 receptor (IL-2-R; p55 or Tac antigen) joined to the transmembrane domain and either full-length or truncated cytoplasmic domain of the human insulin receptor (Ins-R). Expression studies using mouse T cell line EL-4 revealed that the chimeric receptors are able to manifest properties indistinguishable from the authentic IL-2-R. On the other hand, stimulation of the tyrosine kinase activity by IL-2 was not observed in the chimeric receptor with the entire cytoplasmic domain of the Ins-R. These findings thus shed light on the structural conformation and functioning of the IL-2-R complex.

8/7/125
06203984 87177984
A chimeric, ligand-binding v-erbB/EGF receptor retains transforming potential.
Riedel H; Schlessinger J; Ullrich A
Science Apr 10 1987, 236 (4798) p197-200, ISSN 0036-8075
Journal Code: UJ7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Comparison of amino acid sequences from human epidermal growth factor (EGF) receptor and avian erythroblastosis virus erbB oncogene product suggests that v-erbB represents a truncated avian EGF receptor gene product. Although both proteins are transmembrane tyrosine kinases, the v-erbB protein lacks most of the extracellular ligand-binding domain and a 32-amino acid cytoplasmic sequence present in the human EGF receptor. To test the validity of the proposed origin of v-erbB and to investigate the functional significance of the deleted extracellular sequences, a chimeric gene encoding the extracellular and the transmembrane domain of the human EGF receptor joined to sequences coding for the cytoplasmic domain of the avian erbB oncogene product was constructed. When expressed in Rat1 fibroblasts, this reconstituted gene product (HER-erbB) was transported to the cell surface and bound EGF. Its autophosphorylation activity was stimulated by interaction with the ligand. Expression of the HER-erbB chimera led to anchorage-independent cell growth in soft agar and EGF-induced focus formation in Rat1 monolayers. Thus, it appears that v-erbB protein sequences in the chimeric receptor retain their transforming activity under the influence of the human extracellular EGF-binding domain.

9/7/13.
06003479 86304479
Regulation of kinase and intermolecular bonding in intact and truncated epidermal growth factor receptor.
Basu M; Sen-Majumdar A; Basu A; Murthy U; Das M
J Biol Chem Sep 25 1986, 261 (27) p12879-82, ISSN 0021-9258
Journal Code: HIV
Contract/Grant No.: CA-43787; HD-17896
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Tyrosine kinase activity of the epidermal growth factor (EGF) receptor can be regulated by its state of association. Studies done with the purified receptor solubilized in Triton X-100 indicate that dimer formation results in negative regulation of kinase, whereas successive binding of EGF and ATP shift the association equilibrium toward the catalytically active monomeric form. The promotion of the monomeric state by ATP can be mimicked by various nonphosphorylating analogs indicating that nucleotide binding rather than autophosphorylation is responsible for stabilizing the monomeric receptor form. Truncated receptor forms, lacking either the external EGF-binding domain or the internal kinase (ATP-binding) domain, are unable to form stable dimers. These results suggest that both intra- and extracellular domains of the receptor act to stabilize the kinase-regulatory dimer.

8/7/137
05817663 86118663
Similarity of protein encoded by the human c-erb-B-2 gene to epidermal growth factor receptor.
Yamamoto T; Ikawa S; Akiyama T; Semba K; Nomura N; Miyajima N; Saito T; Toyoshima K
Nature Jan 16-22 1986, 319 (6050) p230-4, ISSN 0028-0836
Journal Code: NSC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A novel v-erb-B-related gene, c-erb-B-2, which has been identified in the human genome, maps to human chromosome 17 at q21 (ref. 40), and seems to encode a polypeptide with a kinase domain that is highly homologous with, but distinct from, that of the epidermal growth factor (EGF) receptor. The c-erb-B-2 gene is conserved in vertebrates and it has been suggested that the neu gene, detected in a series of rat neuro/glioblastomas, is, in fact, the rat c-erb-B-2 gene. Amplification of the c-erb-B-2 gene in a salivary adenocarcinoma and a gastric cancer cell line MKN-7 suggests that its over-expression is sometimes involved in the neoplastic process. To determine the nature of the c-erb-B-2 protein, we have now molecularly cloned complementary DNA for c-erb-B-2 messenger RNA prepared from MKN-7 cells. Its sequence shows that the c-erb-B-2 gene encodes a possible receptor protein and allows an analysis of the similarity of the protein to the EGF receptor and the neu product. As a consequence of chromosomal aberration in MKN-7 cells, a 4.6-kilobase (kb) normal transcript and a truncated 2.3-kb transcript of c-erb-B-2 are synthesized at elevated levels. The latter transcript presumably encodes only the extracellular domain of the putative receptor.
?t s10/7/17-21 25

10/7/17
07637700 91156700
Native avian c-erbB gene expresses a secreted protein product corresponding to the ligand-binding domain of the receptor.
Maihle NJ; Flickinger TW; Raines MA; Sanders ML; Kung HJ
Department of Biochemistry and Molecular Biology, Mayo Clinic and Foundation, Rochester, MN 55905.
Proc Natl Acad Sci U S A Mar 1 1991, 88 (5) p1825-9, ISSN 0027-8424
Journal Code: PV3
Contract/Grant No.: CA 51197, CA, NCI; CA 39207, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

A primer-directed cDNA library was used to obtain cDNA clones corresponding to the 5' end (i.e., the ligand-binding domain) of the avian c-erbB gene. Bacterial c-erbB fusion proteins were synthesized and used to obtain polyclonal antisera specific for the ligand-binding domain of the avian receptor. These antisera and antisera specific for the carboxyl terminal domain of the chicken c-erbB gene product have been used to study the native protein products of the c-erbB locus in primary cell cultures by in vivo labeling and immunoprecipitation. Our studies reveal that three c-erbB gene products of Mr 300,000, Mr 170,000, and Mr 95,000 are synthesized in uninfected chicken embryo fibroblasts. Only the Mr 300,000 and Mr 170,000 species can be precipitated by using antisera specific for the cytoplasmic domain of the c-erbB product. The 95,000 species is not recognized by the antiserum directed against the carboxyl-terminal domain of c-erbB and is specifically released into the culture medium. Northern transfer studies reveal a lower molecular weight transcript of approximately 2.6 kilobases that selectively hybridizes to the ligand-binding domain of the avian c-erbB gene product but does not hybridize with probes specific for the cytoplasmic kinase domain of c-erbB. An additional cDNA clone corresponding to this transcript has been isolated, and its sequence suggests it may arise via alternative processing. Together, these data suggest that a truncated form of this growth factor receptor--i.e., a Mr 95,000 species--is synthesized from a low molecular weight c-erbB transcript that exclusively encodes the ligand-binding domain of the receptor. Secretion of truncated growth factor receptors has been reported recently in several systems, and our results are discussed in the light of these findings.

10/7/18
07423671 90330671
Deletion analysis of the human insulin receptor ectodomain reveals independently folded soluble subdomains and insulin binding by a monomeric alpha-subunit.
Schaefer EM; Siddle K; Ellis L
Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas 75235-9050.
J Biol Chem Aug 5 1990, 265 (22) p13248-53, ISSN 0021-9258
Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A series of 13 deletions within the extracellular domain of the human insulin receptor delineates the boundaries of subdomains that fold de novo into stable proteins that are efficiently secreted and retain the epitopes required for interaction with two conformation-specific monoclonal antibodies. While most of these proteins fail to bind insulin, a truncation that includes only the alpha-subunit is secreted as a monomer that binds the hormone with an affinity only slightly less than that of the complete heterotetrameric extracellular domain. These results thus demarcate landmarks within the primary sequence which will now guide further analysis of the structure and function of this complex domain of the receptor.

10/7/19
07423649 90330649
Baculovirus-directed expression of the human insulin receptor and an insulin-binding ectodomain [published erratum appears in J Biol Chem 1990 Nov 15;265(32):20051]
Paul JI; Tavare J; Denton RM; Steiner DF
Howard Hughes Medical Institute, University of Chicago, Illinois 60637.
J Biol Chem Aug 5 1990, 265 (22) p13074-83, ISSN 0021-9258
Journal Code: HIV
Contract/Grant No.: DK 13914, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In this report we describe the use of the baculovirus expression system to overproduce the human insulin holoreceptor (HIR) and a truncated, secretory version of the HIR cDNA (HIRsec) consisting of the alpha subunit and the extracellular portion of the beta subunit (beta'). Sf9 cells

infected with the full-length rHIR viruses synthesize recombinant rHIR (rHIR) with an insulin-binding alpha subunit of apparent Mr = 110,000 and a beta subunit of apparent Mr = 80,000. Uncleaved alpha beta proreceptor accumulates in infected cells. Both of these forms assemble into higher order disulfide-linked dimers or heterotetramers of apparent Mr greater than 350,000. Insulin-binding activity in cells infected with rHIR viruses is present predominantly on the extracellular aspect of the plasma membrane (greater than 80%). Insulin binding to the full-length rHIR occurs with typical complex kinetics with Kd1 = 0.5-1 x 10(-9) M and Kd2 = 10(-7) M and receptors are present in large amounts in infected cells (1 x 10(6) receptors/cell; 1-2 mg HIR/10(9) cells). The full-length rHIR undergoes insulin-dependent autophosphorylation; half-maximal activation of beta subunit autophosphorylation occurs at 1-2 x 10(-8) M. The alpha beta proreceptor also becomes phosphorylated in vitro. Analysis of tryptic phosphopeptides derived from in vitro autophosphorylated beta subunit and alpha beta proreceptor reveals a pattern of phosphorylation that is indistinguishable from that of authentic placental HIR. Sf9 cells infected with rHIRsec viruses synthesize and secrete an (alpha beta')2 heterotetrameric complex having an insulin-binding alpha subunit of apparent Mr = 110,000 and a truncated beta' subunit of apparent Mr = 45,000 that lacks kinase activity. The rHIRsec complex purified from the conditioned medium of infected cells binds insulin with high affinity (Kd = 10(-9) M).

10/7/20
07351888 90258888

A truncated, secreted form of the epidermal growth factor receptor is encoded by an alternatively spliced transcript in normal rat tissue.

Petch LA; Harris J; Raymond VW; Blasband A; Lee DC; Earp HS
Department of Pharmacology, University of North Carolina 27599.

Mol Cell Biol Jun 1990, 10 (6) p2973-82, ISSN 0270-7306
Journal Code: NGY
Contract/Grant No.: DK-30002, DK, NIDDK; CA-43793, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Two independent cDNA clones corresponding to a 2.7-kilobase (kb) epidermal growth factor receptor (EGF-R) mRNA were isolated from a rat liver cDNA library. Sequence analysis revealed 100% homology in the external domain when compared with the full-length rat EGF-R nucleotide sequence and 80 to 90% similarity relative to the human EGF-R. However, the 3'-terminal sequence of these clones did not match EGF-R or any other known sequence(s) and was distinct from the 3' end of the 2.8-kb mRNA, which encodes a truncated EGF-R in A431 cells. The deduced amino acid sequence revealed an open reading frame which is homologous to the external domain of the EGF-R but which terminates prior to the transmembrane region. Southern blot analysis of rat genomic DNA indicated that the 3'-terminal sequence of this transcript is derived from the EGF-R gene. Analysis of a genomic clone containing the 3' end of the 2.7-kb transcript revealed that this sequence is present as a discrete exon in the mid-region of the receptor gene in proximity to the exon encoding the transmembrane domain. Introduction of an expression vector containing the truncated EGF-R cDNA into Chinese hamster ovary (CHO) cells led to the expression of a 95-kilodalton protein which was detected in conditioned media, by using antisera directed against the EGF-R. A similarly sized protein was also detected in the media of WB cells, a continuous, nontransformed line of rat hepatic epithelial cells. Northern (RNA blot) analysis established that the truncated receptor is encoded by a 2.7-kb transcript found in normal rat liver. Furthermore, Northern analysis of rat poly(A)+ RNA showed that the 2.7-kb EGF-R transcript is expressed at differing levels in various fetal and adult tissues. These data indicate that alternative splicing of the EGF-R primary transcript yields a 2.7-kb mRNA which codes for a truncated form of the receptor. This receptor is secreted by rat hepatic epithelial cells in culture, which suggests that it may be secreted by normal rat cells or tissues and perhaps serve an as yet unknown physiological function.

10/7/21
07327495 90234495
Truncation of the ectodomain of the human insulin receptor results in secretion of a soluble insulin binding protein from transfected CHO cells.
Ellis L; Sissom J; Levitan A
Howard Hughes Medical Institute, Dallas, TX.
J Mol Recognit Feb 1988, 1 (1) p25-31, ISSN 0952-3499
Journal Code: A00
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The insulin receptor is an integral transmembrane glycoprotein comprised of two alpha-(approximately 135 kDa) and two beta-(approximately 95 kDa) subunits, which is synthesized as a single polypeptide chain precursor (alpha beta). The primary sequence of the human insulin receptor (hIR) protein, deduced from the nucleotide sequence of cloned human placental mRNAs, predicts two large domains (929 and 403 residues) on either side of a single membrane spanning domain (23 residues); each of these major domains has a distinct function (insulin binding and protein/tyrosine kinase activity, respectively). To experimentally test this deduced topology, and to explore the potential for independent domain function by the hIR extracellular domain, we have constructed an expression plasmid encoding an hIR deletion mutant which is truncated 8 residues from the beginning of the predicted transmembrane domain (i.e., 921 residues). This domain of the hIR is in fact processed into alpha- and truncated beta-subunits and secreted with high efficiency from transfected CHO cell lines which express this mutant hIR, and the protein accumulates as an (alpha beta)2 dimer in the medium. This molecule is recognized by a battery of 13 monoclonal antibodies to epitopes on the IR extracellular domain, four of which block insulin binding and two of which require the native conformation of the IR for recognition. Further, this domain binds insulin with an apparent dissociation constant comparable to that of the wild-type hIR. However, the secreted dimer displays a linear Scatchard plot, while that of the wild-type membrane-associated hIR is curvilinear. (ABSTRACT TRUNCATED AT 250 WORDS)

10/7/25
07072077 89374077
Secretion of the extracellular domain of the human insulin receptor from insect cells by use of a baculovirus vector.
Sissom J; Ellis L
Howard Hughes Medical Institute, Dallas, TX.
Biochem J Jul 1 1989, 261 (1) p119-26, ISSN 0264-6021
Journal Code: 9Y0
Languages: ENGLISH
Document type: JOURNAL ARTICLE
To explore the utility of the baculovirus/insect-cell system for the expression of a soluble secreted human insulin-receptor (hIR) extracellular ligand-binding domain, we have engineered a recombinant virus encoding an hIR deletion mutant which is truncated eight residues from the beginning of the predicted transmembrane domain (i.e. 921 residues). Within 24 h after infection of Sf9 cells with virus, insulin-binding activity begins to accumulate in the culture medium, and reaches a maximum between 48 and 72 h. The intracellular transit and processing of this secreted receptor, designated 'AchIR01', is quite slow. After 24 h in pulse-chase experiments approximately 50% of the metabolically labelled protein is still inside the cell. This protein accumulates as a non-cleaved hIR precursor which is glycosylated, but the carbohydrate is entirely endoglycosidase H (endoH)-sensitive (i.e. high mannose). Approximately one-half of the receptor in the culture medium (i.e. approximately 25% of the total) is in the form of non-cleaved precursor, and about one half of its carbohydrate chains are now endoH-resistant. The remainder of the protein is proteolytically processed hIR (alpha-plus truncated beta-subunits). None of these hIR species exhibit O-linked carbohydrate. Only the processed form of the receptor in the medium binds insulin. This insulin-binding protein is secreted as a dimer (alpha beta)2, and binds insulin with an affinity which is comparable with that of both the wild-type hIR as well as the secreted

form of the hIR expressed in mammalian cells. Despite the rather inefficient processing and altered glycosylation of the AchIR01 protein in insect cells, this high-affinity insulin-binding protein accumulates in the medium at levels (mg/litre) of about 100 times that achieved in a mammalian-cell system.
?t s12/7/13

12/7/13
06686114 88331114
Cell surface expression of glycosylated, nonglycosylated, and truncated forms of a cytoplasmic protein pyruvate kinase.
Hiebert SW; Lamb RA
Department of Biochemistry, Molecular Biology and Cell Biology, Northwestern University, Evanston, Illinois 60208.
J Cell Biol Sep 1988, 107 (3) p865-76, ISSN 0021-9525
Journal Code: HMV
Contract/Grant No.: AI-20201; AI-23173
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The soluble cytoplasmic protein pyruvate kinase (PK) has been expressed at the cell surface in a membrane-anchored form (APK). The hybrid protein contains the NH2-terminal signal/anchor domain of a class II integral membrane protein (hemagglutinin/neuraminidase, of the paramyxovirus SV5) fused to the PK NH2 terminus. APK contains a cryptic site that is used for N-linked glycosylation but elimination of this site by site-specific mutagenesis does not prevent cell surface localization. Truncated forms of the APK molecule, with up to 80% of the PK region of APK removed, can also be expressed at the cell surface. These data suggest that neither the complete PK molecule nor its glycosylation are necessary for intracellular transport of PK to the cell surface, and it is possible that specific signals may not be needed in the ectodomain of this hybrid protein to specify cell surface localization.
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$1.00 DIALNET
$6.50 Estimated cost this search
$6.50 Estimated total session cost 0.083 Hrs.

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File 351:DERWENT WORLD PATENTS INDEX-LATEST
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S1          52   HER2 OR NEU OR P185 OR C(W)ERBB
S2          28   INSULIN(W)RECEPTOR OR (IGF OR INSULIN(W)LIKE(W)GROWTH(W)FA-
             CTOR)(W)RECEPTOR
S3          43   (EGF OR EPIDERMAL(W)GROWTH(W)FACTOR)(W)RECEPTOR
S4         115   S1 OR S2 OR S3
S5       11757   TRUNCAT?
S6           2   S4 AND S5
S7      754464   EXTRACELLULAR OR EXTERNAL OR SURFACE OR LIGAND(W)BINDING OR
              HYDROPHILIC OR (AMINO OR N)(W)TERMINAL
S8           1   S6 AND S7
S9        5981   SECRET?
S10          0   S8 AND S9
S11          2   ECTODOMAIN
S12          0   S5 AND S11 NOT S8

?t s6/7/1-2

 6/7/1
009502761  WPI Acc No: 93-196297/24
XRAM Acc No: C93-087034
    New epidermal growth factor receptor truncate proteins - which bind
    ligands of EGF receptor without transmitting signal for growth or
    reproduction
Patent Assignee: (WARN ) WARNER LAMBERT CO
Author (Inventor): CONNORS R W
Number of Patents: 001
Number of Countries: 001
Patent Family:
    CC Number    Kind     Date      Week
    US 5218090      A      930608     9324   (Basic)

Priority Data (CC No Date): US 536896 (900612); US 604728 (901026)
Abstract (Basic): US 5218090  A
          An epidermal growth factor (EGF) receptor truncate protein
    selected from LD1D2D3 ApaL, LD2D3D4 and LD3D4 having EGD binding sites
    is claimed.
          USE/ADVANTAGE - The truncate proteins bind ligands of the EGF
    receptor without transmitting a signal for the growth and reproduction
    of a cell. They can be used as absorptive agents for any moieties that
    bind the EGF receptor such as EGF and TGF-alpha and viruses that use
    the EGF receptor as the portal of entry to a cell. The proteins will
    compete with the EGF receptor present on the cell surface for binding
    of the ligands and thereby inhibit the action of the ligands or prevent
    entry of viruses into cells. The proteins can also be used as for the
    EGF receptor itself, such as in the detection of abnormalities in
    mammalian cell growth. The proteins are also useful for prepg. novel
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receptors for efficient detn. of ligands and their antagonists or agonists. Dwg.0/12
Derwent Class: B04; D16;
Int Pat Class: C07K-013/00; C12N-015/12

6/7/2
0004369735 WPI Acc No: 85-196613/32
XRAM Acc No: C85-085921
XRPX Acc No: N85-147490
Diagnosis of neoplastic and related diseases by assay of human test sample for altered or abnormally expressed growth factor receptors or for M-RNA transcripts of genes encoding them
Patent Assignee: (ICRF-) ICRF PATENTS LTD; (YEDA) YEDA RES & DEV CO LTD; (GETH) GENENTECH INC; (WATE/) WATERFIELD M D
Author (Inventor): SCHLESSINGER J; ULLRICH A; WATERFIELD M D; SCHLESSING J; WATERFIELD M
Number of Patents: 006
Number of Countries: 013
Patent Family:

CC	Number	Kind	Date	Week	
WO	8503357	A	850801	8532	(Basic)
AU	8539340	A	850809	8543	
EP	171407	A	860219	8608	
JP	61501168	W	860612	8630	
US	4933294	A	900612	9031	
EP	491675	A1	920624	9226	

Priority Data (CC No Date): GB 842379 (840130); GB 85538 (850109)
Applications (CC,No,Date): EP 92101700 (850130); WO 85GB45 (850130); EP 85900716 (850130); JP 85500645 (850130); US 783951 (851202)
Language: English
EP and/or WO Cited Patents: No-citns.; 11Jnl.Ref; 10Jnl.Ref
Designated States
(National): AU; JP; US
(Regional): AT; BE; CH; DE; FR; GB; LI; LU; NL; SE
Filing Details: EP0491675 Related to EP 171407
Abstract (Basic): WO 8503357
(1) Antibody capable of binding a predetermined aminoacid sequence within the epidermal growth factor (EGF) receptor is new. (2) Antigenic analogue comprising an immunogenic polymer bound to a polypeptide fragment of the EGF receptor is new. (3) DNA or RNA encoding the EGF receptor or a fragment of it is new. (4) DNA or RNA capable of hybridising with DNA or RNA encoding the EGF receptor or a fragment of it is new. (5) Diagnostic procedure comprises obtg. a test sample from a human and assaying it for structurally altered or abnormally expressed growth factor receptors, or for the mRNA transcripts or genes encoding them.
USE/ADVANTAGE - The diagnostic test with body fluids, tissues, etc. is carried out at the protein, RNA, or DNA level. Structural alterations of human EGF receptor and its gene, or in transcription and expression of the gene can be involved in tumourgenesis. The assays are therefore useful in the determn. and control of tumours in humans. The antibodies etc. are used in the diagnostic test. The antigenic analogues are useful in drug targetting and with the polypeptide fragments, may be used to inhibit the activity of normal or abnormal ECF receptors expressed in cancer cells. The polypeptides provide a basis for construction of synthetic oligonucleotides encoding them.
@(72pp Dwg.No.0/8)@
Abstract (US): 9031 US 4933294
Diagnosis for the detection of abnormalities in mammalian cell growth comprises obtg. a test sample from a human and assaying the sample of a truncated epidermal growth factor receptor having at least a portion of its mature amino terminus deleted, and correlating detection of the truncated growth factor receptor with abnormal growth control in mammalian cells.
USE/ADVANTAGE - Neoplastic and other diseases can be diagnosed by

assaying e.g. body fluid, tissue or cultured tumour explant cells for structurally altered or abnormally expressed growth factor receptors. @(25pp)@
Derwent Class: B04; C03; D16; S03; R16;
Int Pat Class: A61K-039/39; A61K-039/395; A61K-049/00; C07K-007/04; C07K-015/00; C12P-021/00; C12Q-001/68; G01N-033/57; G01N-033/574

?s s4 and s7
115 S4
754464 S7
S13 24 S4 AND S7
t s13/7/8 12 18 19 24

13/7/8
009072174 WPI Acc No: 92-199589/24
Related WPI Accession(s): 92-123385; 93-188588; 93-226664
XRAM Acc No: C92-090853
Nucleic acid encoding polypeptide fusions - comprising ligand binding partner protein and immunoglobulin chain, for use in diagnosis and therapy
Patent Assignee: (GETH) GENENTECH INC
Author (Inventor): CAPON D J; LASKY L A
Number of Patents: 001
Number of Countries: 001
Patent Family:

CC	Number	Kind	Date	Week	
US	5116964	A	920526	9224	(Basic)

Priority Data (CC No Date): US 315015 (890223); US 440625 (891122)
Abstract (Basic): US 5116964 A
The following are claimed: (A) nucleic acid encoding a polypeptide fusion comprising a ligand binding partner protein (LBPP) contg. more than one polypeptide chain, where LBPP is not a platelet growth factor receptor or an insulin receptor, one of the chains being fused to an immunoglobulin constant region through C- or N-terminal amino or carboxyl gps.; (B) nucleic acid encoding a polypeptide fusion of a LBPP and an immunoglobulin chain, where the LBPP is not a platelet growth factor receptor or an insulin receptor, the LBPP and the immunoglobulin chain being fused through C- or N-terminal amino or carboxyl gps., and the fusion further comprising an additional fusion of an agent selected from a multiple subunit (chain) polypeptide, a portion of an immunoglobulin superfamily member, a toxin and a polypeptide therapeutic agent not otherwise associated with an immunoglobulin, and an immunoglobulin chain; (C) nucleic acid encoding a polypeptide fusion comprising a LBPP which comprises a lymphocyte cell surface glycoprotein (LHR) and an immunoglobulin chain, in which the LBPP and immunoglobulin are fused through C- or N-terminal amino or carboxyl gps..

USE - The fusion of the immunoglobulin chain to the LBPP prolongs the in vivo plasma half-life of the LBPP and facilitates its purification. The polypeptide fusions combine the adhesive and targeting characteristics of the LBPP with immunoglubulin effector functions such as complement binding and cell receptor binding. They can be used therapeutically or as diagnostic reagents for the in vitro assay of LBPPs or their targets. In particular, the LHR-immunoglobulin hybrid is used therapeutically to compete with the normal binding of lymphocyte to lymphoid tissue. The hybrid is therefore useful for organ or graft rejection, for treatment of inflammation, e.g. due to rheumatoid arthritis or other autoimmune diseases, for control of lymphoma metastasis, in treating conditions in which there is an accumulation of lymphocytes and for targeting therapeutic moieties to lymphoid tissues, eg. for treating tissues infected with viruses such as HIV Dwg.0/10
Derwent Class: B04; D16;
Int Pat Class: C07H-021/04; C12N-015/62; C12P-021/02

13/7/17
008849755 WPI Acc No: 91-353773/48
XRAM Acc No: C91-152614
XRPX Acc No: N91-270909
New hybrid cellular receptor - has 2 sequences encoding extracellular domain of receptors having different ligand binding specificity e.g. insulin- and IGF-receptors
Patent Assignee: (NOVO) NOVO-NORDISK AS; (NOVO) NOVO NORDISK A/S
Author (Inventor): ANDERSEN A; KJELDSEN T; MOELLER N P; RASMUSSEN J; WIBERG F; ANDERSEN A S; KJELDSEN T B; MOELLER N P H; RASMUSSEN J S; WIBERG F C ; KJEDSEN T; MOLLER N
Number of Patents: 004
Number of Countries: 026
Patent Family:

CC	Number	Kind	Date	Week	
WO	9117252	A	911114	9148	(Basic)
AU	9177921	A	911127	9210	
FI	9204890	A	921028	9304	
EP	528878	A1	930303	9309	

Priority Data (CC No Date): DK 901063 (900430); DK 901855 (900803)
Applications (CC,No,Date): EP 91909103 (910430); WO 91DK115 (910430); WO 91DK115 (910430); FI 924890 (921028)
Language: English
EP and/or WO Cited Patents: 3.Jnl.Ref; EP 325262
Designated States
(National): AU; BG; CA; FI; HU; JP; KR; NO; PL; RO; SU; US
(Regional): AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LI; LU; NL; SE
Filing Details: EP0528878 Based on WO 9117252
Abstract (Basic): WO 9117252

A hybrid DNA construct (I), comprising a 1st sequence (Ia) encoding part of the extracellular domain of a 1st cellular receptor and a 2nd sequence (Ib) encoding part of the extracellular domain of a 2nd cellular receptor is new. The two receptors are specific for different ligands.

Also claimed are (1) a hybrid polypeptide (A) encoded by (I), (2) a recombinant expression vector comprising (I), (3) a cell contg. the vector of (2), (4) a process for producing (A) comprising culturing the cell of (3) in a suitable nutrient medium under conditions conductive to expression of (A) and recovering (A) from the culture, (5) a method for identifying the ligand-binding site on a cellular receptor utilising (A), incubated with ligands specific for the receptors, with binding between both detected, and (6) a polypeptide fragment of the extracellular domain of a cellular receptor.

Pref. the sequence of (A) which is a hybrid insulin/insulin-like growth Factor-I (IGF-I) receptor is given in the specification in addn. to the CDNA sequence encoding it.

USE - (A) is useful for screening for ligands or functional equivalents (claimed method) as well as for localising ligand-binding sites. It is also useful for establishing the 3-D structure of the ligand-binding site and designing an analogue or functional equivalent. @(97pp Dwg.No.0/7)@

Derwent Class: B04; D16; S03;
Int Pat Class: C12N-005/00; C12N-015/62; G01N-033/53

13/7/18
008569503 WPI Acc No: 91-073538/10
XRAM Acc No: C91-031175
XRPX Acc No: N91-056832
C-erbB-2 external domain gps. proteins, antibodies, etc. - for use in vaccines, diagnosis and treatment of neoplastic disease
Patent Assignee: (TRIT-) TRITON BIOSCIENCES INC; (TRIT-) TRITON BIOSCI INC
Author (Inventor): STUART S G; MONAHAN J J; LANGTON B C; HANCOCK M E; CHAO L A; BLUFORD P
Number of Patents: 004
Number of Countries: 016

Patent Family:

CC	Number	Kind	Date	Week	
WO	9102062	A	910221	9110	(Basic)
AU	9064135	A	910311	9123	
EP	444181	A	910904	9136	
JP	4503012	W	920604	9229	

Priority Data (CC No Date): US 389920 (890804)
Applications (CC,No,Date): JP 90513165 (900802); WO 90US4340 (900802); EP 90914094 (900802)
Language: English
EP and/or WO Cited Patents: NoSR.Pub
Designated States
(National): AU; CA; JP
(Regional): AT; BE; CH; DE; DK; ES; FR; GB; IT; LU; NL; SE; LI
Filing Details: JP04503012 Based on WO 9102062
Abstract (Basic): WO 9102062

The following are claimed:- (1) A recombinant DNA molecule coding for the external domain of the c-erba-2 protein (gp.75) or its fragment linked to an expression control sequence. (2) A prokaryotic or eukaryotic host cell transformed with the DNA. Cells include: E. coli, Pseudomonas, Bacillus, yeast, other fungi, animal, insect and plant cells. (3) Recombinant gp. 75 proteins which are glycosylated and serologically active; and their production by transforming a unicellular host with recombinant DNA. (4) Monoclonal and polyclonal antibodies to the proteins which may be used in treatment of neoplastic disease. (5) A method of testing mammalian body fluids for presence of gp. 75 especially for detection of breast adenocarcinoma or ovarian adenocarcinoma, and (6) A vaccine comprising substantially pure gp. 75 proteins or cell membranes containing the proteins to immunise a human against neoplastic disease.

USE/ADVANTAGE - For detection of the external domain of c-erbB-2 and gp.75 in diagnosis of neoplastic disease. Also for prophylaxis and treatment of tumours that express the c-erbB-2 oncogene. @(91pp Dwg.No.0/15)@

Derwent Class: B04; D16; R16;
Int Pat Class: A61K-033/24; A61K-037/02; A61K-039/00; C07K-013/00; C07K-015/00; C12N-001/19; C12N-005/10; C12N-009/12; C12N-015/12; C12P-021/08; G01N-033/53; G01N-035/53

13/7/19
008488946 WPI Acc No: 90-375946/50
XRAM Acc No: C90-163774

HER2 extracellular domain used as vaccine - comprises sequence of at least 9 aminoacid(s) prepd. using expression vector of DNA isolated from human epidermal growth factor receptor

Patent Assignee: (GETH) GENENTECH INC
Author (Inventor): HUDZIAK R M; SHEPARD H M; ULLRICH A
Number of Patents: 002
Patent Family:

CC	Number	Kind	Date	Week	
WO	9014357	A	901129	9050	(Basic)
EP	474727	A	920318	9212	

Priority Data (CC No Date): US 354319 (890519)
Applications (CC,No,Date): WO 90US2697 (900518); EP 90908809 (900518)
Language: English
EP and/or WO Cited Patents: US 4761371; 5.Jnl.REF
Designated States
(National): CA
(Regional): AT; BE; CH; DE; DK; ES; FR; GB; IT; LU; NL; SE; LI
Filing Details: EP0474727 Based on WO9014357 (PT)
Abstract (Basic): WO 9014357

An extracellular portion of HER2 molecule comprises at least 9 amino acids and is an immune epitope, which is at least 99% pure being free of transmembrane and intracellular portions of HER2 molecule. The extracellular portion is antigenic in animals and is conjugated with a

peptide having immunogenic properties. Preparation of extracellular portion comprises ligating a DNA isolate of at least 9 amino acids terminated upstream of the portion encoding the transmembrane or intracellular portions of the HER2 molecule, into an expression vector to transform a suitable host which when cultured under suitable conditions gives rise to the extracellular portion.

USE/ADVANTAGE - Preparing vaccines from the extracellular domains of host cell. @(48pp Dwg.No.0/13)@

Derwent Class: B04; D16;
Int Pat Class: C07K-007/06; C07K-013/00; C07K-017/00; C12N-001/19; C12N-005/10; C12N-015/12; A61K-039/00; C12P-021/02

13/7/24
007820435 WPI Acc No: 89-085547/11
XRAM Acc No: C89-037987

Recombinant pox virus expressing tumour-associated antigen - used as vaccines against tumour cells and for producing antibodies for immunotherapy or diagnosis

Patent Assignee: (BIOT-) APPL BIOTECHN INC; (WHIT-) WHITEHEAD INST BIOMED RES
Author (Inventor): PANICALI D L; BERNARDS R
Number of Patents: 001
Patent Family:

CC	Number	Kind	Date	Week	
WO	8901973	A	890309	8911	(Basic)

Priority Data (CC No Date): US 92036 (870902)
Applications (CC,No,Date): WO 88US3032 (880901)
Language: English
EP and/or WO Cited Patents: No.SR.Pub; GB 2188637; 8.Jnl.REF
Designated States
(National): JP
(Regional): AT; BE; CH; DE; FR; GB; IT; LU; NL; SE
Abstract (Basic): WO 8901973

A recombinant pox virus capable of expressing in a host a cell-encoded, tumour-associated antigen is claimed. The pox virus is pref. a vaccinia virus. The tumour antigen may be encoded by the neu gene, the ros gene, the trk gene, the kit gene or a portion of these or the antigen may be a growth factor receptor or growth factor receptor-like cell surface molecule.

USE/ADVANTAGE - The live recombinant viruses can be used to induce an immune response, both humoral and cell-mediated, against tumour cells which express the protein. They can also be used to produce antibody against the antigen for use in therapeutics or diagnostics. The antibodies may be useful in passive immunotherapy against tumour. They may also be used to quantify the antigen in a biological fluid. Cells incected in vitro with the recombinant pox viruses can be used as a source of tumour associated antigens. @(46pp Dwg.No.0/4)@

Derwent Class: B04; D16;
Int Pat Class: A61K-039/00; C12N-015/00
?log hold
20sep93 10:32:30 User208669 Session D543.6
$6.53 0.033 Hrs File351
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$15.53 Estimated cost File351
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DIALNET: call cleared by request

Enter Service:

3/3/112 (Item 2 from file: 399)
119007204 CA: 119(9)87204s JOURNAL
Real-time measurements of kinetics of EGF binding to soluble EGF receptor monomers and dimers support the dimerization model for receptor activation
AUTHOR(S): Zhou, M.; Felder, S.; Rubinstein, M.; Hurwitz, D. R.; Ullrich, A.; Lax, I.; Schlessinger, J.
LOCATION: Med. Cent., New York Univ., New York, NY, 10016, USA
JOURNAL: Biochemistry DATE: 1993 VOLUME: 32 NUMBER: 32 PAGES: 8193-8
CODEN: BICHAW ISSN: 0006-2960 LANGUAGE: English

3/3/113 (Item 3 from file: 399)
112176923 CA: 112(19)176923y PATENT
Monoclonal antibodies against the HER2 receptor, and their use in treating tumor cells
INVENTOR(AUTHOR): Hudziak, Robert M.; Shepard, H. Michael; Ullrich, Axel
LOCATION: USA
ASSIGNEE: Genentech, Inc.
PATENT: PCT International ; WO 8906692 A1 DATE: 890727
APPLICATION: WO 89US51 (890105) *US 143912 (880112) *US 147461 (880125)
PAGES: 52 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12P-021/00A; C12N-015/00B; C12N-005/00B; G01N-033/574B; A61K-039/395B
DESIGNATED COUNTRIES: JP

3/3/114 (Item 1 from file: 351)
009174662 WPI Acc No: 92-302096/37
XRAM Acc No: C92-134631
XRPX Acc No: N92-231094
Recombinant antibodies directed to growth factor receptor C-ERBB-2 - for diagnosing and treating tumours expressing C-ERBB-2 e.g. breast or ovarian tumours
Patent Assignee: (CIBA) CIBA GEIGY AG
Author (Inventor): GRONER B; HARDMAN N; HARWERTH I; HYNES N E; WELS W S; ZWICKL M
Patent Family:

CC Number	Kind	Date	Week	
EP 502812	A1	920909	9237	(Basic)
AU 9210421	A	920813	9240	
CA 2060544	A	920806	9243	

Priority Data (CC No Date): EP 91810079 (910205)
Applications (CC,No,Date): EP 92810056 (920127); AU 9210421 (920123); CA 2060544 (920203)

3/3/115 (Item 2 from file: 351)
008488946 WPI Acc No: 90-375946/50
XRAM Acc No: C90-163774
HER2 extracellular domain used as vaccine - comprises sequence of at least 9 aminoacid(s) prepd. using expression vector of DNA isolated from human epidermal growth factor receptor
Patent Assignee: (GETH) GENENTECH INC
Author (Inventor): HUDZIAK R M; SHEPARD H M; ULLRICH A
Patent Family:

CC Number	Kind	Date	Week	
WO 9014357	A	901129	9050	(Basic)
EP 474727	A	920318	9212	

Priority Data (CC No Date): US 354319 (890519)
Applications (CC,No,Date): WO 90US2697 (900518); EP 90908809 (900518)

3/3/116 (Item 3 from file: 351)
007968734 WPI Acc No: 89-233842
XRAM Acc No: C89-104136

3/3/106 (Item 18 from file: 5)
6475909 BIOSIS Number: 850[illegible]30
RELEASE OF TISSUE-TYPE PLASMINOGEN ACTIVATOR IS INDUCED IN RATS BY LEUKOTRIENES C-4 AND D-4 BUT NOT BY PROSTAGLANDINS E-1 E-2 AND I-2
TRANQUILLE N; EMEIS J J
GAUBIUS INST. TNO, HERENSTR. 5D, 2313 AD LEIDEN, NETH.
BR J PHARMACOL 93 (1). 1988. 156-164. CODEN: BJPCB
Full Journal Title: British Journal of Pharmacology
Language: ENGLISH

3/3/107 (Item 19 from file: 5)
5889729 BIOSIS Number: 84022294
GRAY PLATELET SYNDROME STUDIES ON PLATELET ALPHA-GRANULES LYSOSOMES AND DEFECTIVE RESPONSE TO THROMBIN
SRIVASTAVA P C; POWLING M J; NOKES T J C; PATRICK A D; DAWES J; HARDISTY R M
DEP. HAEMATOL./ONCOL., HOSP. SICK CHILDREN, GREAT ORMOND ST., LONDON WC1N 3JH.
BR J HAEMATOL 65 (4). 1987. 441-446. CODEN: BJHEA
Full Journal Title: British Journal of Haematology
Language: ENGLISH

3/3/108 (Item 20 from file: 5)
5884122 BIOSIS Number: 84016687
A CHIMERIC LIGAND-BINDING V-ERB-B-EGF RECEPTOR RETAINS TRANSFORMING POTENTIAL
RIEDEL H; SCHLESSINGER J; ULLRICH A
DEP. DEV. BIOL., GENENTECH INC., 460 POINT SAN BRUNO BLVD., SAN FRANCISCO, CALIF. 94080, USA.
SCIENCE (WASH D C) 236 (4798). 1987. 197-200. CODEN: SCIEA
Language: ENGLISH

3/3/109 (Item 21 from file: 5)
4885305 BIOSIS Number: 80012616
THE DROSOPHILA EPIDERMAL GROWTH FACTOR RECEPTOR GENE HOMOLOGUE CONSERVATION OF BOTH HORMONE BINDING AND KINASE DOMAINS
LIVNEH E; GLAZER L; SEGAL D; SCHLESSINGER J; SHILO B-Z
DEP. CHEM. IMMUNOL., WEIZMANN INSTITUTE OF SCIENCE, REHOVOT 76100, ISRAEL.
CELL 40 (3). 1985. 599-608. CODEN: CELLB
Full Journal Title: Cell
Language: ENGLISH

3/3/110 (Item 22 from file: 5)
4458457 BIOSIS Number: 78032280
ANTIGEN INITIATED RELEASE OF PLATELET ACTIVATING FACTOR PAF-ACETHER FROM MOUSE BONE MARROW DERIVED MAST CELLS SENSITIZED WITH MONO CLONAL IMMUNO GLOBULIN E
MENCIA-HUERTA J-M; LEWIS R A; AUSTEN K F; RAZIN E
DEP. MED., HARVARD MED. SCH., BOSTON, MA 02115.
J IMMUNOL 131 (6). 1983. 2958-2964. CODEN: JOIMA
Full Journal Title: Journal of Immunology
Language: ENGLISH

3/3/111 (Item 1 from file: 399)
119087291 CA: 119(9)87291t JOURNAL
Decreased level of PDGF-stimulated receptor autophosphorylation by fibroblasts in mechanically relaxed collagen matrixes
AUTHOR(S): Lin, Ying Chun; Grinnell, Frederick
LOCATION: Southwest. Med. Sch., Univ. Texas, Dallas, TX, 75235, USA
JOURNAL: J. Cell Biol. DATE: 1993 VOLUME: 122 NUMBER: 3 PAGES: 663-72
CODEN: JCLBA3 ISSN: 0021-9525 LANGUAGE: English

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*     The USPTO production files are current through:                     *
*      07 MAR 1995 for U.S. Patent Text Data.                             *
*      07 MAR 1995 for U.S. Current Classification data.                  *
*      07 MAR 1995 for U.S. Patent Image Data.                            *
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FILE 'USPAT' ENTERED AT 16:21:40 ON 07 MAR 95

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 *                  W E L C O M E   T O   T H E                          *
*          U. S.   P A T E N T   T E X T   F I L E                       *
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=> s (human epidermal growth factor receptor 2) or her2 or ngl or
(c(w)erbb?) or erbb?           113366 HUMAN
            2500 EPIDERMAL
          101383 GROWTH
          193084 FACTOR
           16115 RECEPTOR
         1389356 2

               0 HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2

(HUMAN(W)EPIDERMAL(W)GROWTH(W)FACTOR(W)RECEPTOR(W)2)
               3 HER2
             150 NGL
         1023325 C
              41 ERBB?
              10 C(W)ERBB?
              41 ERBB?
L1           192 (HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2) OR HER2
OR NGL O R (
                 C(W)ERBB?) OR ERBB?

=> s l1 and domain?
          21629 DOMAIN?
L2           26 L1 AND DOMAIN?

=> s l2 and (extracellular or transmembran? or cytoplasm?)
    3703 EXTRACELLULAR
            1233 TRANSMEMBRAN?
            2048 CYTOPLASM?
L3             22 L2 AND (EXTRACELLULAR OR TRANSMEMBRAN? OR
CYTOPLASM?)
=> s l3 and soluble
          171037 SOLUBLE
L4              5 L3 AND SOLUBLE

=> s l3 not l4
L5             17 L3 NOT L4

=> d l4 1-5

1.  5,367,060, Nov. 22, 1994, Structure, production and use of
heregulin; Richard L. Vandlen, et al., 530/399, 350 [IMAGE
```

AVAILABLE]

2. 5,344,760, Sep. 6, 1994, Method of cancer detection; Jeanne P. Harvey, et al., 435/7.5, 7.1, 7.9, 7.92; 436/501, 518, 536 [IMAGE AVAILABLE]

3. 5,256,642, Oct. 26, 1993, Compositions of **soluble** complement receptor 1 (CR1) and a thrombolytic agent, and the methods of use thereof; Douglas T. Fearon, et al., 514/8; 424/94.63, 94.64; 435/215, 216; 514/2; 530/350 [IMAGE AVAILABLE]

4. 5,243,041, Sep. 7, 1993, DNA vector with isolated CDNA gene encoding metallopanstimulin; Jose A. Fernandez-Pol, 536/23.5, 24.31 [IMAGE AVAILABLE]

5. 5,212,071, May 18, 1993, Nucleic acids encoding a human C3b/C4b receptor (CR1); Douglas T. Fearon, et al., 435/69.1, 252.3, 320.1; 530/350 [IMAGE AVAILABLE]

=> d l4 1,2 ab

US PAT NO: 5,367,060 [IMAGE AVAILABLE] L4: 1 of 5

ABSTRACT:
A novel polypeptide with binding affinity for the p185.sup.**HER2** receptor, designated heregulin-.alpha., has been identified and purified from cultured human cells. DNA sequences encoding additional heregulin polypeptides, designated heregulin-.alpha., heregulin-.beta.1, heregulin-.beta.2, heregulin-.beta.2-like, and heregulin-.beta.3, have been isolated, sequenced and expressed. Provided herein are nucleic acid sequences encoding the amino acid sequences of heregulins useful in the production of heregulins by recombinant means. Further provided are the amino acid sequences of heregulins and purification methods therefor. Heregulins and their antibodies are useful as therapeutic agents and in diagnostic methods.

US PAT NO: 5,344,760 [IMAGE AVAILABLE] L4: 2 of 5

ABSTRACT:
Diagnostic/prognostic methods are provided for detecting and/or quantitating in the body fluids, preferably serum, of mammals carrying a malignant tumor burden, elevated levels of a portion of the epidermal growth factor receptor (EGFr) which comprises substantially the EGFr ectodomain having a molecular weight in the range of from about 90 kilodaltons (kd) to about 115 kd, preferably from about 95 kd to about 105 kd, and more preferably about 100 kd. Substantially pure compositions comprising said EGFr ectodoman protein and/or fragments thereof are disclosed as well as test kits for performing the disclosed assays.
=> d l5 1-17

1. 5,376,530, Dec. 27, 1994, Steroid/thyroid hormone receptor-related gene, which is inappropriately expressed in human heptocellular carcinoma, and which is a retinoic acid

receptor; Hughes B. De The, et al., 435/6, 69.1, 172.3; 530/326, 327, 350, 828; 536/23.1, 24.31 [IMAGE AVAILABLE]

2. 5,317,090, May 31, 1994, Steroid/thyroid hormone receptor-related gene, which is inappropriately expressed in human hepatocellular carcinoma, and which is a retinoic acid receptor; Hughes Blaudin De The, et al., 530/387.1, 387.9, 388.1, 388.22, 391.1 [IMAGE AVAILABLE]

3. 5,288,477, Feb. 22, 1994, Method for prognosticating response to cancer therapy; Sarah S. Bacus, 424/2, 85.5; 435/7.1; 436/501 [IMAGE AVAILABLE]

4. 5,223,606, Jun. 29, 1993, Steroid/thyroid hormone receptor-related protein inappropriately expressed in human hepatocellular carcinoma; Hughes Blaudin de The, et al., 530/350; 435/69.1; 530/828, 846 [IMAGE AVAILABLE]

5. 5,212,290, May 18, 1993, Antibodies specific for type II mutant EGTR; Bert Vogelstein, et al., 530/387.7, 387.1, 388.22, 388.8, 389.1 [IMAGE AVAILABLE]

6. 5,183,884, Feb. 2, 1993, DNA segment encoding a gene for a receptor related to the epidermal growth factor receptor; Matthias H. Kraus, et al., 536/23.5; 435/252.3, 320.1; 536/23.1 [IMAGE AVAILABLE]

7. 5,149,731, Sep. 22, 1992, Steroid/thyroid hormone receptor-related gene inappropriately expressed in human hepatocellular carcinoma; Hugues Blaudin de THE, et al., 530/326, 327, 328, 350, 405 [IMAGE AVAILABLE]

8. 5,030,576, Jul. 9, 1991, Receptors for efficient determination of ligands and their antagonists or agonists; Thomas J. Dull, et al., 435/69.7, 69.1; 530/350, 388.22; 536/23.1, 24.1 [IMAGE AVAILABLE]

9. 4,968,603, Nov. 6, 1990, Determination of status in neoplastic disease; Dennis J. Slamon, et al., 435/6, 7.23; 436/94, 501; 935/77, 78 [IMAGE AVAILABLE]

10. 4,957,865, Sep. 18, 1990, Cloning or expression vectors containing the avian erythroblastosis virus genome and cells transfected by these vectors; Jacques Samarut, et al., 435/235.1, 69.1, 317.1, 320.1; 935/32, 57 [IMAGE AVAILABLE]

11. 4,937,232, Jun. 26, 1990, Inhibition of protein kinase C by long-chain bases; Robert M. Bell, et al., 514/26, 28; 536/5 [IMAGE AVAILABLE]

12. 4,935,341, Jun. 19, 1990, Detection of point mutations in neu genes; Cornelia I. Bargmann, et al., 435/6, 803; 436/501; 536/24.3, 24.31; 935/9, 78 [IMAGE AVAILABLE]

13. 4,933,294, Jun. 12, 1990, Method of detecting truncated epidermal growth factor receptors; Michael D. Waterfield, et al., 436/501; 435/4, 7.21, 7.23, 15; 436/503, 518, 813, 815, 817 [IMAGE AVAILABLE]

domains of the EGF-R and **erbB**-2 proteins, respectively. cDNA cloning revealed a predicted 148 kd **transmembrane** polypeptide with structural features identifying it as a member of the **erbB** family, prompting designation of the new gene as **erbB**-3. It was mapped to human chromosome 12q11-13 and was shown to be expressed as a 6.2 kb transcript in a variety of normal tissues of epithelial origin. Markedly elevated **erbB**-3 mRNA levels were demonstrated in certain human mammary tumor cell lines. These findings indicate that increased **erbB**-3 expression, as in the case of EGF-R and **erbB**-2, plays a role in some human malignancies.

US PAT NO: 4,935,341 [IMAGE AVAILABLE] L5: 12 of 17
ABSTRACT:
Oligonucleotide probes reactive with regions of neu oncogenes of mammalian origin in which the mutation causing activation of such oncogenes is contained are described, as are methods for their use in detecting the presence of neu oncogenes in tumor cells. Antibodies specific for gene products encoded by neu oncogenes are also described.

US PAT NO: 4,933,294 [IMAGE AVAILABLE] L5: 13 of 17
ABSTRACT:

Neoplastic and other diseases can be diagnosed by assaying a human test sample e.g. body fluid, tissue or cultured tumor explant cells, for structurally altered or abnormally expressed growth factor receptors or for the RNA transcripts of genes which encode them. For example, the assay can be for truncated EGF receptor having at least a portion of its mature amino terminus deleted. Antibodies, capable of binding a predetermined amino acid sequence within the EGF receptor, are also useful in diagnosis and therapy as are conjugates of an immunogenic polymer bound to a polypeptide fragment of EGF receptor. DNA and RNA encoding EGF receptor or fragments thereof are also described.

=> d his

(FILE 'USPAT' ENTERED AT 16:21:40 ON 07 MAR 95)
L1 192 S (HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2) OR HER2 OR NG
L 0
L2 26 S L1 AND DOMAIN?
L3 22 S L2 AND (EXTRACELLULAR OR TRANSMEMBRAN? OR CYTOPLASM?)
L4 5 S L3 AND SOLUBLE
L5 17 S L3 NOT L4

=> log y
U.S. Patent & Trademark Office LOGOFF AT 16:29:29 ON 07 MAR 95
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OK
ATH

OK

14. 4,859,609, Aug. 22, 1989, Novel receptors for efficient determination of ligands and their antagonists or agonists; Thomas J. Dull, et al., 436/501; 435/7.22, 7.31, 7.9, 960; 436/63, 503, 537; 530/402, 806, 808; 935/81, 109 [IMAGE AVAILABLE]

15. 4,837,237, Jun. 6, 1989, Therapy using glucosidase processing inhibitors; Larry R. Rohrschneider, et al., 514/62; 436/63, 64; 514/23, 283, 345, 729, 738 [IMAGE AVAILABLE]

16. 4,816,450, Mar. 20, 1989, Inhibition of protein kinase C by long-chain bases; Robert M. Bell, et al., 514/25, 23, 26, 28, 54; 536/5 [IMAGE AVAILABLE]

17. 4,774,321, Sep. 27, 1988, DP100 EGF and insulin-binding protein from Drosophila cells; Marsha R. Rosner, et al., 530/350; 436/501; 530/303, 305, 389.1, 389.2, 399, 413 [IMAGE AVAILABLE]

=> d l5 3,6,12,13 ab

US PAT NO: 5,288,477 [IMAGE AVAILABLE] L5: 3 of 17

ABSTRACT:

A method for prognosticating the effectiveness of a chemotherapy using monoclonal antibodies and ligand molecules. The putative anti-cancer agent has binding specificity for a oncogenic receptor molecule on the membrane of a cancer cell, such as HER-2/neu. When the putative agent binds to the oncogenic receptor, the receptor translocates from the membrane to the **cytoplasm** or perinucleus of the cancer cell, accompanied by a transient increase in the total cellular content of the receptor, and results in terminal cell differentiation. The efficacy of the agent in vivo can be determined in vitro by treatment of biopsied cancer cells with the agent and subsequent examination of the cells for evidence of terminal cell differentiation. Such evidence includes morphological change, reduction in cell growth, or production of chemicals associated with the mature phenotype. Additionally, treated cells may be examined with immunohistochemicals specific for the oncogenic receptor, to determine translocation of the receptor from the membrane to the **cytoplasm** or perinucleus. Quantification of receptor levels in treated cells by measuring optical densities after staining can be used to determine translocation, as well as a transient increase in total cellular content of the receptor.

US PAT NO: 5,183,884 [IMAGE AVAILABLE] L5: 6 of 17

ABSTRACT:

A DNA fragment distinct from the epidermal growth factor receptor (EGF-R) and **erbB**-2 genes was detected by reduced stringency hybridization of v-**erbB** to normal genomic human DNA. Characterization of the cloned DNA fragment mapped the region of v-**erbB** homology to three exons with closest homology of 64% and 67% to a contiguous region within the tyrosine kinase

MONOCLONAL ANTIBODIES DIRECTED AGAINST THE EXTRACELLULAR DOMAIN OF THE HER2-ERBB2
KOTTS C E; WIRTH C M; CARVER M E; FENDLY B M
GENENTECH INC., DEP. MEDICINAL ANALYTICAL CHEMISTRY, S. SAN FRANCISCO, CALIF. 94080.
FORTY-FIRST ANNUAL MEETING OF THE TISSUE CULTURE ASSOCIATION, HOUSTON, TEXAS, USA, JUNE 10-13, 1990. IN VITRO CELL DEV BIOL 26 (3 PART 2). 1990. 59A. CODEN: ICDBE
Language: ENGLISH
Document Type: CONFERENCE PAPER

3/3/101 (Item 13 from file: 5)
7044909 BIOSIS Number: 87105430
P185 +HER-2 MONOCLONAL ANTIBODY HAS ANTIPROLIFERATIVE EFFECTS IN-VITRO AND SENSITIZES HUMAN BREAST TUMOR CELLS TO TUMOR NECROSIS FACTOR
HUDZIAK R M; LEWIS G D; WINGET M; FENDLY B M; SHEPARD H M; ULLRICH A
DEP. DEV. BIOL., GENENTECH INC., 460 POINT SAN BRUNO BLVD., SOUTH SAN FRANCISCO, CALIF. 94080.
MOL CELL BIOL 9 (3). 1989. 1165-1172. CODEN: MCEBD
Full Journal Title: Molecular and Cellular Biology
Language: ENGLISH

3/3/102 (Item 14 from file: 5)
6974775 BIOSIS Number: 87035296
BIOCHEMICAL AND PHARMACOLOGICAL CHARACTERIZATION OF HUMAN EMBRYO-DERIVED PLATELET ACTIVATING FACTOR
COLLIER M; O'NEILL C; AMMIT A J; SAUNDERS D M
HUMAN REPRODUCTION UNIT, ROYAL NORTH SHORE HOSP., ST. LEONARDS, NSW 2065, AUST.
HUM REPROD (OXF) 3 (8). 1988. 993-998. CODEN: HUREE
Full Journal Title: Human Reproduction (Oxford)
Language: ENGLISH

3/3/103 (Item 15 from file: 5)
6640197 BIOSIS Number: 86106748
PHOSPHOLIPASE A-2 INDUCED AIRWAY HYPERREACTIVITY TO COOLING AND ACETYLCHOLINE IN RAT TRACHEA PHARMACOLOGICAL MODULATION
CHAND N; DIAMANTIS W; MAHONEY T P; SOFIA R D
DEP. PHARMACOLOGY, WALLACE LAB., DIV. CARTER-WALLACE INC., CRANBURY, N.J. 08512.
BR J PHARMACOL 94 (4). 1988. 1057-1062. CODEN: BJPCB
Full Journal Title: British Journal of Pharmacology
Language: ENGLISH

3/3/104 (Item 16 from file: 5)
6633430 BIOSIS Number: 86099981
TRANSIENT INCREASE OF CYTOSOLIC FREE CALCIUM IN CULTURED HUMAN VASCULAR ENDOTHELIAL CELLS BY PLATELET-ACTIVATING FACTOR
HIRAFUJI M; MAEYAMA K; WATANABE T; OGURA Y
DEP. PHARMACOL., TOHOKU UNIV. SCH. DENTISTRY, 4-1 SEIRYO-MACHI, SENDAI 980, JPN.
BIOCHEM BIOPHYS RES COMMUN 154 (3). 1988. 910-917. CODEN: BBRCA
Full Journal Title: Biochemical and Biophysical Research Communications
Language: ENGLISH

3/3/105 (Item 17 from file: 5)
6617729 BIOSIS Number: 86084280
ROLE OF PAF-ACETHER IN THE MEDIATION OF PATHOPHYSIOLOGICAL RESPONSES TO AGGREGATED IMMUNOGLOBULINS STUDIES WITH THE PLATELET-ACTIVATING FACTOR RECEPTOR ANTAGONIST BN-52021
FERNANDEZ-GALLARDO S; CANO E; BRAQUET P; SANCHEZ CRESPO M
INST. INVEST. MED. FUND. JIMENEZ DIAZ, CENT. ASOCIADO CSIC, AV. REYES CATOLICOS 2, 28040-MADRID, SPAI
INT J IMMUNOPHARMACOL 10 (4). 988. 353-360. CODEN: IJIMD
Full Journal Title: International Journal of Immunopharmacology
Language: ENGLISH

CANCER RESEARCH INST., UNIVERSITY CALIFORNIA, SAN FRANCISCO, CALIF. 94143-0128.
J BIOL CHEM 266 (22). 1991. 14300-14305. CODEN: JBCHA
Full Journal Title: Journal of Biological Chemistry
Language: ENGLISH

3/3/95 (Item 7 from file: 5)
8211582 BIOSIS Number: 91132582
SELECTION OF MONOCLONAL ANTIBODIES WHICH INDUCE INTERNALIZATION AND PHOSPHORYLATION OF P185H-E-R-2 AND GROWTH INHIBITION OF CELLS WITH HER2-NEU GENE AMPLIFICATION
TAGLIABUE E; CENTIS F; CAMPIGLIO M; MASTROIANNI A; MARTIGNONE S; PELLEGRINI R; CASALINI P; LANZI C; MENARD S; COLNAGHI M I
DIV. EXP. ONCOL. E, ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI, VIA G. VENEZIAN 1, 20133 MILAN, ITALY.
INT J CANCER 47 (6). 1991. 933-937. CODEN: IJCNA
Full Journal Title: International Journal of Cancer
Language: ENGLISH

3/3/96 (Item 8 from file: 5)
8165749 BIOSIS Number: 91086749
SCINTIGRAPHIC DETECTION OF OVEREXPRESSED C-ERB-B-2 PROTOONCOGENE PRODUCTS BY A CLASS-SWITCHED MURINE ANTI-C-ERB-B-2 PROTEIN MONOCLONAL ANTIBODY
SAGA T; ENDO K; AKIYAMA T; SAKAHARA H; KOIZUMI M; WATANABE Y; NAKAI T; HOSONO M; YAMAMOTO T; ET AL
DEP. NUCL. MED., KYOTO UNIV. HOSP., SHOGOIN, SAKYO-KU, KYOTO 606, JPN.
CANCER RES 51 (3). 1991. 990-994. CODEN: CNREA
Full Journal Title: Cancer Research
Language: ENGLISH

3/3/97 (Item 9 from file: 5)
7761575 BIOSIS Number: 90129575
DISTINCT STIMULATORY EFFECT OF PLATELET-ACTIVATING FACTOR ON PROSTAGLANDIN I-2 AND THROMBOXANE A-2 BIOSYNTHESIS BY RAT DENTAL PULP
HIRAFUJI M; OGURA Y
DEP. PHARMACOL., TOHOKU UNIV. SCH. DENT., 4-1 SEIRYO-MACHI, SENDAI 980, JPN.
EUR J PHARMACOL 185 (1). 1990. 81-90. CODEN: EJPHA
Full Journal Title: European Journal of Pharmacology
Language: ENGLISH

3/3/98 (Item 10 from file: 5)
7743434 BIOSIS Number: 90111434
ELISA FOR QUANTITATION OF THE EXTRACELLULAR DOMAIN OF P185H-E-R-2 IN BIOLOGICAL FLUIDS
SIAS P E; KOTTS C E; VETTERLEIN D; SHEPARD M; WONG W L T
IMMUNOL. RES. ASSAY TECHNOLOGIES, GENENTECH INC., 460 POINT SAN BRUNO BLVD., SOUTH SAN FRANCISCO, CALIF. 94080, USA.
J IMMUNOL METHODS 132 (1). 1990. 73-80. CODEN: JIMMB
Full Journal Title: Journal of Immunological Methods
Language: ENGLISH

3/3/99 (Item 11 from file: 5)
7678519 BIOSIS Number: 90046519
PHARMACOLOGICAL MODULATION OF 2 METHYLCARBAMATE PAF INDUCED RAT PAW EDEMA
CASTRO-FARIA-NETO H C; SILVA P M R; MARTINS M A; SILVA P S; HENRIQUES M G O M; CORDEIRO R S B; VARGAFTIG B B
DEP. FISIOLOGIA FARMACODINAMICA, FUNDACAO-OSWALDO CRUZ, AV. BRASIL, 4365 MANGUINHOS, 20010 RIO DE JANEIRO, RJ, BRAZ.
J PHARM PHARMACOL 42 (3). 1990. 203-204. CODEN: JPPMA
Full Journal Title: Journal of Pharmacy and Pharmacology
Language: ENGLISH

3/3/100 (Item 12 from file: 5)
7563000 BIOSIS Number: 39075607
DIFFERENTIAL GROWTH INHIBITION OF HUMAN CARCINOMA CELLS EXPOSED TO

Languages: ENGLISH
Document type: JOURNAL ARTICLE

3/3/89 (Item 1 from file: 5)
10453588 BIOSIS Number: 96053588
ANTIBODY-INDUCED ACTIVATION OF P185H-E-R-2 IN THE HUMAN LUNG ADENOCARCINOMA CELL LINE CALU-3 REQUIRES BIVALENCY
SRINIVAS U; TAGLIABUE E; CAMPIGLIO M; MENARD S; COLNAGHI M I
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Full Journal Title: Cancer Immunology Immunotherapy
Language: ENGLISH

3/3/90 (Item 2 from file: 5)
10278981 BIOSIS Number: 45078981
A RECOMBINANT SINGLE CHAIN FV FUSION MOLECULE SPECIFICALLY RECOGNIZES THE EXTRACELLULAR DOMAIN OF THE ERBB-2 RECEPTOR
WELS W; HARWERTH I-M; GRONER B; HYNES N E
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Language: ENGLISH
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3/3/91 (Item 3 from file: 5)
9546122 BIOSIS Number: 94051122
VLA-4-FIBRONECTIN INTERACTION IS REQUIRED FOR THE TERMINAL DIFFERENTIATION OF HUMAN BONE MARROW CELLS CAPABLE OF SPONTANEOUS AND HIGH RATE IMMUNOGLOBULIN SECRETION
ROLDAN E; GARCIA-PARDO A; BRIEVA J A
HOSP. RAMON Y CAJAL, SERVICIO DE INMUNOLOGIA, 28034 MADRID, SPAIN.
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Full Journal Title: Journal of Experimental Medicine
Language: ENGLISH

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8826738 BIOSIS Number: 42051738
DETECTION OF TRUNCATED AND ALTERNATIVELY SPLICED TRANSCRIPTS CONTAINING HER2-NEU EXTRACELLULAR DOMAIN IN HUMAN BREAST CANCER CELLS
ROBLES R; SCOTT G K; TRIPATHY D; PARKS J; SHEPARD H M; BENZ C C
CANCER RESEARCH INST., UNIV. CALIFORNIA, SAN FRANCISCO, CALIF. 94143.
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8673109 BIOSIS Number: 92138109
REQUIREMENTS FOR THE INTERNALIZATION OF A MURINE MONOCLONAL ANTIBODY DIRECTED AGAINST THE HER-2-NEU GENE PRODUCT C-ERB-B-2
MAIER L A; XU F J; HESTER S; BOYER C M; MCKENZIE S; BRUSKIN A M; ARGON Y; BAST R C JR
BOX 3843, DUKE UNIV. MED. CENT., DURHAM, N.C. 27710, USA.
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SCOTT G K; DODSON J M; MONTGOMERY P A; JOHNSON R M; SARUP J C; WONG W L; ULRICH A; SHEPARD H M; BENZ C C

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Languages: ENGLISH
Document type: JOURNAL ARTICLE

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Department of Virology, University of Helsinki, Finland.

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Service d'Endocrinologie Pediatrique, Hopital Saint-Vincent-de-Paul, Paris.
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Departments of Pathology, Duke University Medical Center, Durham, NC 27710.
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Department of Medicine, University of Alabama, Birmingham 35294.
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Journal Code: A0W
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Vincent T. Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, DC 20007.
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Section of Molecular Carcinogenesis, Institute of Cancer Research, Sutton, Surrey, UK.
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Laboratory of Cellular and Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892.
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Department of Pharmacology, Cornell University, Ithaca, NY 14853-6401.
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Department of Chemical Immunology, Weizmann Institute of Science, Rehovot, Israel.
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Alternative splicing of the Schistosoma mansoni gene encoding a homologue of epidermal growth factor receptor.
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Department of Tropical Public Health, Harvard School of Public Health, Boston, MA 02115.
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[Role of p185c-erbB2 in endometrial cancer growth in vitro]
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Department of Obstetrics and Gynecology, Nihon University, Faculty of Medicine, Tokyo.
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Department of Biochemistry, Molecular, and Cell Biology, Cornell University, Ithaca, New York 14853-6401.
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Department of Medicine, Pennsylvania State University College of Medicine, Milton S. Hershey Medical Center, Hershey, PA 17033.
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Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111.
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Department of Biomedical Science and Oncology, University of Torino Medical School, Italy.
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Department of Developmental Biology, Genentech, Inc., South San Francisco, California 94080.
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Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

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Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA 98121.
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Section of Immunology, Institute of Cancer Research, Sutton, Surrey, UK.
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Laboratory of Cell Biology, Food and Drug Administration, Bethesda, Maryland 20892.
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Taglienti-Sian CA; Banner B; Davis RJ; Robinson HL
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Languages: ENGLISH
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Institute of Cell Biology (Cancer Research), University of Essen Medical School, Germany.
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Ruder Boskovic Institute, Laboratory of Molecular Oncology, Zegreb, Croatia.
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University of Southern California School of Medicine 90054-0700.
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Contract/Grant No.: DK31036, DK, NIDDK; DK43123, DK, NIDDK; DK36836, DK, NIDDK
Languages: ENGLISH
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Howard Hughes Medical Institute, National Jewish Center for Immunology and Respiratory Medicine, Denver, CO.
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